A Facile Synthesis Route to Decyl-(*R*)-2-Methylbutyl-Dichlorosilane as a Monomer of Rigid-Rod Helical Polysilane

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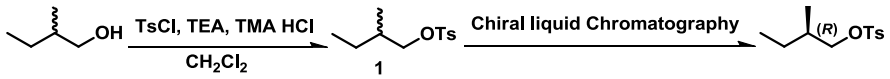
We have developed a 9-step synthesis route to decyl-(*R*)-2-methylbutyl-dichlorosilane, a monomer of right-handed helical polysilane, whose chiral starting material is not commercially available unlike its *S*-isomer. The synthesis of the *R*-isomer has never been reported although it has been long-awaited to investigate the prospective chiral resolution of the right- and left handed helical rigid-rod polymers. The key step of the synthesis is the protection of the hydroxyl group in stereochemically pure methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate, which was used as a commercially available starting material, with a tetrahydropyranyl group, followed by the reduction of ester group and the tosylation of resulting hydroxyl group to give (*R*)-2-methylbutyl-2-tetrahydropyranyl ether. The stereochemistry of the materials has been confirmed to be retained throughout the process by chiral HPLC, GC, and optical rotation measurements.
Key words: stereochemistry, monomer synthesis, chiral resolution, polysilane, chiral HPLC

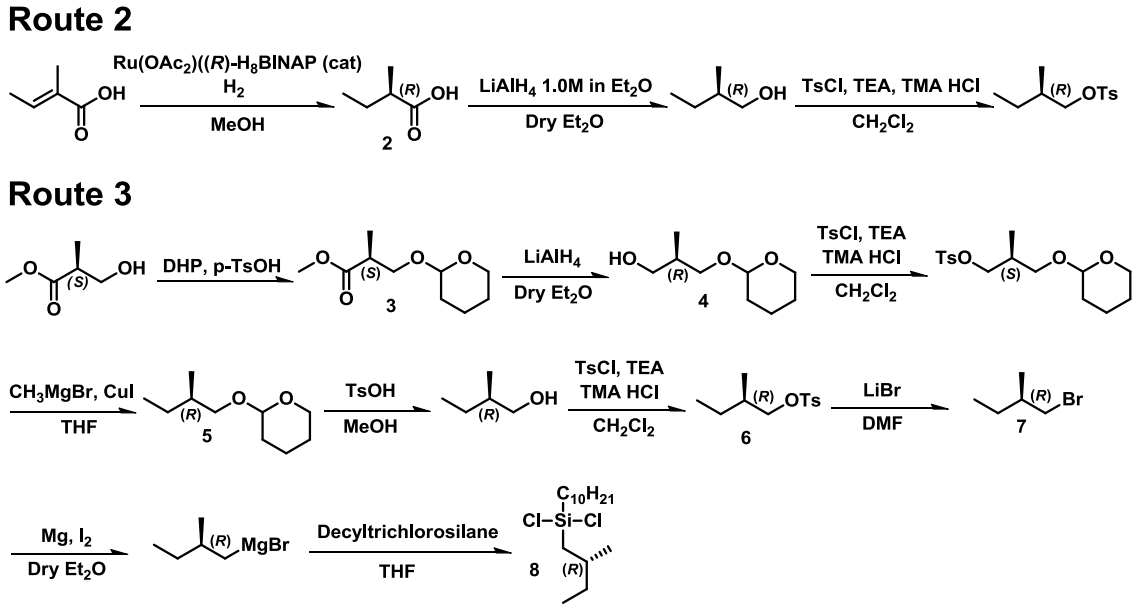
1. INTRODUCTION

Due to the broken chiral symmetry in nature, the optical resolution of materials that lead to a chirally asymmetric state is of great interest in every field of material science. Since Pasteur has reported the separation of the racemic mixture into enantiomers by separating individual crystals [1], which has later led to the selective crystallization of one isomer in the solution of racemic mixture with the seed crystal of one isomer, optical resolutions of countless chemicals have been achieved not only based on the crystallization but also chromatography utilizing the diastereomeric interactions of racemic compounds modified by chiral derivatizing agents. Along with the tremendous efforts for the development of asymmetrical syntheses, the situation has been totally changed in recent years by the successful development of chiral stationary phases for liquid chromatography to separate the optically pure enantiomers from their racemic mixtures.

For many years, we have been working on the polysilanes with (*S*)-2-methyl-butyl side chain which form a right-handed helical main chain conformation [2-5]. This polymer has extremely stiff main chain for this kind of synthetic polymers due to large steric hinderance between the bulky side chains so that it forms a smectic liquid crystal phase when sufficiently narrowed the molecular weight distributions. Lately, we have been interested in the optical resolution of the racemic mixtures of right- and left-handed helical polysilanes because we have found the segregation of polysilanes with different lengths (molecular weights) and widths (side chain lengths) due to the entropic effects based on the rigid body repulsion. However, the starting chiral material for left handed helical polysilane, (*R*)-2-methyl-butyl-bromide is not commercially available. Therefore, in this study, we have attempted to synthesize the monomer of left handed helical polysilane with (*R*)-2-methyl-butyl side chain, decyl-(*R*)-2-methyl-butyl-dichlorosilane by following three synthetic routs: 1. chiral separation of racemic 2-methyl-butyl tosylate by preparative chiral liquid chromatography, 2. catalytic asymmetric hydrogenation of tiglic acid, 3. 9 step synthesis starting from methyl-(*S*)-(+)-3-hydroxy- 2-methylpropionate.

Route 1





Scheme 1. Synthetic routes to decyl-(*R*)-2-methyl-butyl-dichlorosilane

2. RESULTS and DISCUSSION

2.1 Route 1

2.1.1 Synthesis of 2-Methyl-1-butyl-p-toluenesulfonate (**1**)

(*DL*)-2-methy-l-butanol (5.04 g, 57.17 mmol) and triethylamine (11.54 mL, 83.01 mmol) were placed in a 100-mL flask and stirred in an ice bath under dry nitrogen atmosphere. To the solution was added dichloromethane solution (60 mL) of trimethylamine hydrochloride (0.54 g, 5.65 mmol) and p-toluenesulfonyl chloride (13.03 g, 68.35 mmol). After stirring for 1 h, the mixture was poured into 1mol/L HCl aqueous solution (20 ml) to neutralize the remaining amine in a separating funnel, then the organic layer was washed with $NaHCO_3$ aqueous solution (50 ml) and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 2-Methyl-1-butyl-p- toluenesulfonate (**1**) 12.46 g, 90% yield, ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 7.79 (d, *J* =8.4 Hz, 2H), 7.34 (d, *J* =8.0 Hz, 2H), 3.90-3.79 (m, 2H), 2.45 (s, 3H), 1.75-1.67 (m, 1H), 1.44-1.34 (m, 1H), 1.20-1.09 (m, 1H), 0.88 (d, *J* =6.8 Hz, 3H), 0.83 (t, *J* =7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 144.58, 133.17, 129.76, 127.86, 74.79, 34.31, 25.39, 21.59, 15.91, 10.91.

(*R*)-2-methyl-butyl p-toluenesulfonate was successfully separated from obtained racemic 2-methyl-butyl p-toluenesulfonate (**1**) by recycling preparative liquid chromatography LC-9204 (Japan Analytical Industry Co., Ltd. Tokyo, Japan) equipped with a UV detector UV-3740 (Japan Analytical Industry) and a Chiral Pack AY-H (Daicel Corp., Osaka, Japan). A solution of n-Hexane (98%) and ethanol (2%) was used as the eluent at a flow rate of 8 mL/min. However, the study has been discontinued because the yield of each injection was 8 mg at most.

2.2 Route 2

2.2.1 Synthesis of (*R*)-2-Methyl-1-butanoic acid (**2**)

The deoxydated methanol solution of tiglic acid (5.08 g, 50.74 mmol) and $Ru(OAc_2)$((*R*)-H_8-BINAP) (48.7 mg, 57.3 μmol) was placed in a 100-mL autoclave. The vessel was sealed under hydrogen of 2 MPa after 20 alternating vacuum-hydrogen flushing steps and stirred at room temperature for 1 day. The mixture was then distilled under reduced pressure to give (*R*)-2-methyl-1-butanoic acid (**2**) (4.93 g, 95% yield). (4.93 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 10.69 (s, broad, 1H), 2.45-2.37 (m, 1H), 1.77-1.66 (m, 1H), 1.56-1.45 (m, 1H), 1.18 (d, *J* =7.2 Hz, 3H), 0.95 (t, *J* =7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 183.46, 40.87, 26.50, 16.33, 11.51.

The obtained sample was injected into a chiral capillary gas chromatography column InertCap CHIRAMIX (GL Science Inc., Tokyo, Japan) to evaluate the enantiomeric excess of (*R*)-isomer as can be seen in Figure 1 (Enantiomeric Excess: 95.7% *R*). However, the study has been discontinued because the enantiomeric excess was not high enough to proceed without further purification with chiral liquid chromatography.

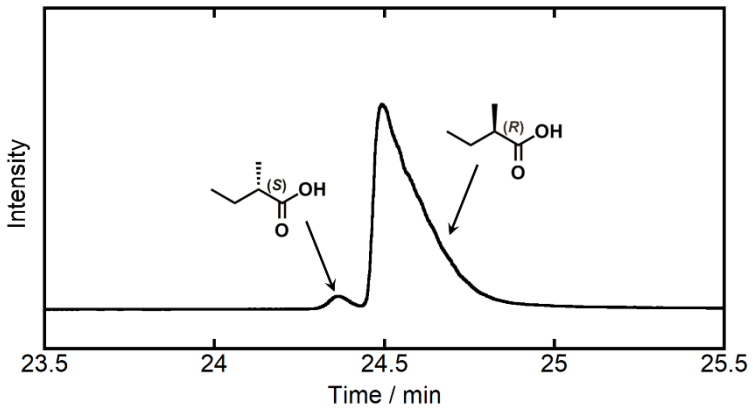


Figure 1. Chiral gas chromatogram of (R)-2-Methyl-1-butanoic acid (**2**)

2.3 Route 3

2.3.1 Synthesis of (2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy) methyl propanoate (**3**)

3,4-dihydro-2H-pyran (6.84 g, 81.31 mmol) and methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate (8.01 g, 67.81 mmol) were placed in 200-mL flask under dry nitrogen atmosphere. To the solution was added p-toluenesulfonic acid monohydride (42.30 mg, 0.22 mmol). After stirring at room temperature for 2 h, the solution was neutralized by adding the saturated aqueous solution of sodium hydrogen carbonate, extracted with diethyl ether several times in a separating funnel, and dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give (2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy) methyl propanoate (**3**) (11.16 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 4.63-4.59 (m, 1H), 3.84-3.74 (m, 2H), 3.70 (s, 3H), 3.62-3.42 (m, 2H), 2.80-2.75 (m, 1H), 1.88-1.50 (m, 6H), 1.20-1.18 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 175.30, 175.22, 98.97, 98.35, 69.30, 68.96, 62.02, 61,71, 51.55, 51.54, 40.14, 39.97, 30.42, 30.35, 25.35, 19.26, 19.04, 13.95, 13.92.

2.3.2 Synthesis of (2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propanoic acid (**4**)

To the diethyl ether solution of lithium aluminum hydride (34 mL (1.0 M), 34.00 mmol) in a 300-mL flask was added dropwise the diethyl ether solution (30 mL) of (2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy) methyl propanoate (**3**) (11.16 g, 55.18 mmol) in an ice bath under dry nitrogen atmosphere and stirred at room temperature for 3 h. The sodium sulfonate decahydrate (10 g) was added to the solution to decompose the remaining lithium aluminum hydride and then the solution was filtrated, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give (2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propanoic acid (**4**) (9.21 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 4.59-4.58 (m, 1H), 3.88-3.33 (m, 6H), 2.66-2.58 (m, 1H), 2.08-1.53 (m, 6H), 0.92-0.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 99.30, 99.03, 72.03, 71.94, 67.22, 67.18, 62.48, 62.43, 35.60, 35.35, 30.54, 30.50, 25.27, 25.24, 19.55, 13.52, 13.41.

2.3.3 Synthesis of 2-((R)-2-methylbutoxy)tetrahydro-2H-pyran (**5**)

(2S)-2-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propyl 4-methylbenzenesulfonate (17.05 g, 51.92 mmol) was dissolved in dry tetrahydrofuran (70 mL) in a 500-mL flask and stirred under dry nitrogen atmosphere. To the solution was added Copper(I)iodide (99%) (310.89 mg, 1.63 mmol) and stirred at -50ºC. Then the diethyl ether solution of methyl magnesium bromide (3M) (54.00ml, 162.00 mmol) was added to the solution and stirred at -50ºC for 1 h, at room temperature overnight, and at 50ºC for 1 h. The cold saturated aqueous solution of ammonium chloride (70 mL) was poured into the solution in an ice bath to quench the remaining methyl magnesium bromide and then the solution was filtrated, extracted with diethyl ether several times in a separating funnel, dried over anhydrous potassium carbonate, and concentrated *in vacuo* to give 2-((R)-2-methylbutoxy)tetrahydro-2H-pyran (**5**) (8.30 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 4.58-4.56 (m, 1H), 3.89-3.13 (m, 6H), 1.87-1.42 (m, 6H), 1.21-1.10 (m, 1H), 0.94-0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 99.00, 98.80, 72.83, 72.72, 62.14, 62.07, 35.00, 34.99, 30.71, 26.31, 26.26, 25.52, 19.58, 19.53, 16.68, 16.55, 11.35, 11.29.

2.3.4 Synthesis of (R)-2-methylbutyl 4-methylbenzenesulfonate (**6**)

2-((R)-2-methylbutoxy)tetrahydro-2H-pyran (**5**) (9.87 g, 52.30 mmol) was dissolved in methanol (140 mL) and stirred at room temperature. To the solution was added p-toluenesulfonic acid monohydride (259.06 mg, 1.36 mmol) to make the solution acidic and stirred at room temperature overnight. After the methanol solution of sodium methoxide (1 M) (1.36 mL, 1.36 mmol) was added to the solution to neutralize it, methanol was evaporated to give (R)-2-methylbutan-1-ol. The crude sample was dissolved

with triethylamine (17.60 g, 173.93 mmol) in dichloromethane and stirred in an ice bath. Trimethylamine hydrochloride (547.40 mg, 5.73 mmol) and dichloromethane solution (60 mL) of p-toluenesulfonyl chloride (16.40 g, 86.20 mmol, 1.6 eq) was added to the solution and stirred in an ice bath for 1 h to form white precipitate. After N,N-dimethylethylenediamine (5 mL) was added to the solution to quench the remaining p-toluenesulfonyl chloride, deionized water was poured into the solution and the organic layer was separated, washed with deionized water and brine in a separating funnel, and dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (neutral silica gel) to give (R)-2-methylbutyl 4-methylbenzenesulfonate (**6**) (10.52 g, 76% yield). $[\alpha]_D^{24}$=−4.75 (c 5.02, Pentane). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 7.79 (d, *J* =8.0 Hz, 2H), 7.35 (d, *J* =8.0 Hz, 2H), 3.90-3.80 (m, 2H), 2.45 (s, 3H), 1.75-1.67 (m, 1H), 1.42-1.34 (m, 1H), 1.20-1.09 (m, 1H), 0.88 (d, *J* =6.8 Hz, 3H), 0.83 (t, *J* =7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 144.62, 133.20, 129.80, 127.91, 74.83, 34.35, 25.43, 21.64, 15.95, 10.95.

The enantiomeric excess of the obtained sample was evaluated by chiral liquid chromatography to show almost no sign of (*S*)-isomer as can be seen in Figure 2

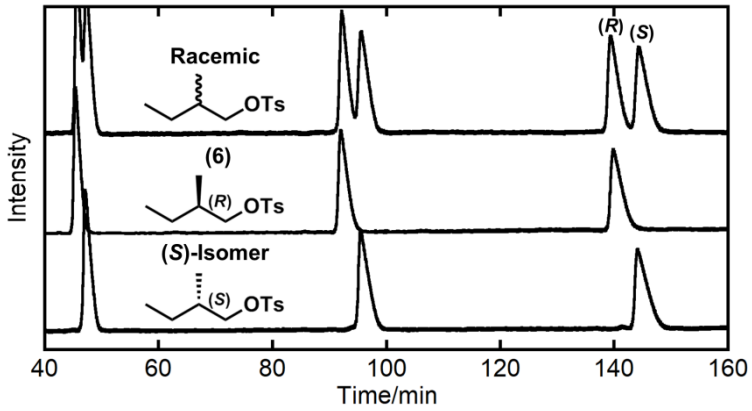


Figure 2. Chiral liquid chromatogram of (R)-2-methylbutyl 4-methylbenzenesulfonate (**6**)

2.3.5 Synthesis of (R)-1-bromo-2-methylbutane (**7**)

Lithium Bromide (13.75 g, Fw:86.84, 158.34.mmol) was dissolved in dry N,N-dimethylformamide (25 mL) under dry nitrogen atmosphere in a 300-mL flask. To the solution was added N,N-dimethylformamide solution (15 mL) of (R)-2-methylbutyl 4-methylbenzenesulfonate (**6**) (18.78 g, 77.50 mmol) and stirred in an ice bath for 1.5 h. After deionized water (50 mL) and then pentane were added to the solution and stirred in an ice bath, upper organic layer was separated, washed with deionized water in a separating funnel, dried over anhydrous magnesium sulfate, filtrated, and concentrated *in vacuo*. The crude product was purified by vacuum distillation to give (R)-1-bromo-2-methylbutane (**7**) (8.68 g, 74% yield).$[\alpha]_D^{24}$=−3.81 (c 6.60, pentane). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 3.42-3.32 (m, 2H), 1.76-1.68 (m, 1H), 1.53-1.44 (m, 1H), 1.33-1.23 (m, 1H), 1.01 (d, *J* =6.8 Hz , 3H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC) δ 41.10, 36.78, 27.57, 18.35, 11.22.

2.3.6 Synthesis of decyl-(*R*)-2-methylbutyl-dichlorosilane (**8**)

Magnesium flakes (2.40 g, 98.72 mmol) were heated to activate the surface under vacuum in a 100-mL flask, flushed with dry nitrogen, added diethyl ether (20 mL) and solid iodine (catalytic amount), and heated to reflux without stirring until the iodine color faded. To the solution was added dropwise the dry diethyl ether solution (50 mL) of (*R*)-1-bromo-2-methyl-butane (11.8 g, 78.13 mmol) at room temperature and stirred at 50ºC for 1 h to give (R)-(2-methylbutyl)magnesium bromide. To the dry tetrahydrofuran solution (25 mL) of n-decyl-trichlorosilane (22.88 g, 83.10.mmol) was added dropwise tetrahydrofuran solution (50 mL) of (R)-(2-methylbutyl)magnesium bromide and stirred at room temperature for 36 h. Magnesium salt was filtrated after adding hexane to the solution and the filtrate was dried over anhydrous magnesium sulfate, filtrated, and concentrated *in vacuo*. The crude product was purified by vacuum distillation to give decyl-(*R*)-2-methylbutyl-dichlorosilane (**8**) (14.97g, 58% yield). $[\alpha]_D^{24}$=−7.99 (neat). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC) δ 1.81-1.73 (m, 1H), 1.54-1.45 (m, 2H),1.43-1.35 (m, 2H), 1.33-1.19 (m, 14H), 1.11-1.07 (m, 2H), 1.02-0.96 (m, 5H), 0.90-0.87 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC)

δ 32.53, 32.37, 31.94, 30.25, 29.63, 29.49, 29.35, 29.25, 28.11, 22.71, 22.46, 21.83, 21.34, 14.11, 11.21.

3. Conclusion

The 9-step synthesis route to decyl-(*R*)-2-methylbutyl-dichlorosilane has been successfully developed with satisfactory optical purity using stereochemically pure methyl-(*S*)-(+)-3-hydroxy-2-methyl-propionate as a commercially available starting material. The enantiomeric excess of the resulting material (**8**) has been evaluated by optical rotation measurement ($[\alpha]_D^{24}$=–7.99 (neat)), which has been reported to be $[\alpha]_D^{24}$=+7.64 (neat) for (*S*) isomer [6], indicating that the stereochemistry of the materials has been retained throughout the process although the optical rotations of (*R*)-2-methylbutyl 4-methyl-benzenesulfonate (**6**) ($[\alpha]_D^{24}$=－4.75 (c 5.02, Pentane)) and (*R*)-1-bromo-2-methylbutane (**7**) ($[\alpha]_D^{24}$=－3.81 (c 6.60, pentane)) were slightly deviated from their (*S*) isomers ($[\alpha]_D^{24}$=+5.31 (c 4.88, pentane) for (*S*)-2-methylbutyl 4-methyl- benzenesulfonate [7] and $[\alpha]_D^{24}$=－3.72 (c 6.56 pentane) for (*S*)-1-bromo-2-methylbutane [8]). These procedures could be applicable for the preparation of optical isomers which will remain indispensable for prospective medical and optical applications.

4. References

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